PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 14286/WO/02	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/00328	International filing date *(day/month/year)* 21.04.2003	Priority date *(day/month/year)* 22.04.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/00		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.11.2003	30.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Covone-van Hees, M.G Telephone No. +31 70 340-4416

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00328

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-41 as originally filed

Claims, Numbers

1-22 received on 17.06.2004 with letter of 15.06.2004

Drawings, Sheets

1/17-17/17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 23-26

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3,9-11,15 (completely)2, 4-6,12,16-22 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 13,14,16-21 (as to I.A.) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3,9-11,15 (completely) 2,4-6,12,16-22 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,7,8,13,14(completely)2,4-6,12,16-22(partially) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,4-8,12-14,16-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,4-8,12-14,16-22
Industrial applicability (IA)	Yes:	Claims	1,4-8,12,22
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

1 The amendments filed with the letter dated 15.06.04 introduce subject-matter which extends beyond the content of the application as filed, contrary to Art. 34(2)(b) PCT. The amendments concerned are the following:
Claim 1: "at least one" (could be interpreted as binds to both)
Claim 2: "at least one" and reference to a substance binding to the HIV-1 protein Tat (not limited to the nuclear localization signal (NLS) of Tat).
The IPEA considers that in the application as filed there is no basis for these amendments, consequently examination will be carried out as if present amendments had not been made. In particular claim 2 will be examined as referring to a substance binding to the nuclear localization signal of the HIV-1 protein Tat

2 Please note that according to the sequence listing seq.ID 1,3 and 5 is a nucleic acid sequence and seq.ID 2,4 and 6 is an amino acid sequence. Therefore claim 7 and 8 have been examined taking into account that the CDR3 have an **amino acid** of any one of seq. ID 2,4 and 6 and the **nucleic acid** of any one of seq. ID 1,3 and 5.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 According to R.66.1(e) PCT claims 2,3,9-11,15 (completely) 4-6,12,16-22 (partially) relating to unsearched subject-matter will not be examined.

2 Claims 13,14,16-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

This Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1,13,14 (completely) 4-8,12,16-22 (partially) directed to a substance that specifically binds nuclear localization signal (NLS) of the HIV-1 Vpr, related (pharmaceutical) compositions, vaccine, related methods according to claims 13,14,16-21.

II: Claims 2,3,9-11,15 (completely) 4-8,12,16-22 (partially) directed to a substance that specifically binds nuclear localization signal (NLS) of the HIV-1 Tat, related (pharmaceutical) compositions, vaccine, related methods according to claims 15-21.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:
A priori the common linking technical feature may be seen as blocking nuclear import of viral genome by targeting nuclear localization signal (NLS)-containing molecules and more specifically the provision of "substances" that bind NLS-containing molecules and thereby block their nuclear import.
However, at the priority date of the present application the concept of targeting NLS to prevent nuclear import of viral genome and substances which bind to NLS containing molecules thereby blocking their nuclear import are known in the art.
Dubrovsky et al. (1995) (D2) teaches the use of substances (arylene bis(methyl ketone) compounds) binding to the NLS of the viral matrix protein of HIV and thereby specifically block translocation of the pre-integration complex (PIC) into the nucleus of non-dividing cells. Targeting of the NLS may be a general effective approach in order to prevent or treat HIV infection (see pg. 217).
The objective remaining problem of the application is the provision of alternative compounds, specifically binding NLS, thereby blocking the nuclear import. The solution is the provision of scFv binding to NLS of Vpr or a peptide derived from the bacteriophage fd p8 protein binding to NLS of Tat. These compounds are not linked by any common structural feature.
As no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special technical feature on which an unifying concept for the present inventions could be based, there is no single inventive concept underlying the claimed inventions of the present application.
The requisite unity of invention (Rule 13.1 PCT) does no longer exist.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

EXAMINATION OF THE FIRST INVENTION:

1 Reference is made to the following documents:

D1: WO 00/49038 A (WRAY VICTOR ;HENKLEIN PETER (DE); SCHUBERT ULRICH (DE)) 24 August 2000 (2000-08-24)

D2: DUBROVSKY LARISA ET AL: "Nuclear localization signal of HIV-1 as a novel target for therapeutic intervention." MOLECULAR MEDICINE (CAMBRIDGE), vol. 1, no. 2, 1995, pages 217-230, ISSN: 1076-1551

D3: WO 99/28338 A (YISSUM RES DEV CO ;GILON CHAIM (IL); FRIEDLER ASSAF (IL); LOYTER A) 10 June 1999 (1999-06-10)

2 **NOVELTY** (Art. 33(2) PCT)

2.1 D1 discloses the production of peptides of the HIV-1 protein Vpr (e.g. sVPR21-40 comprising the nuclear localization signal (NLS) in the N-terminal domain) and their uses. Antibodies specifically binding to these peptides are claimed (see claims 2,7,10,11), but described only in a theoretical manner. In view of the prior art cited the subject-matter of claims 1, 4-8,12-14,16-22 is new (Art.33(2) PCT).

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 The subject-matter of claim 1 contravenes the requirements of Art.33(3) PCT. Claim 1 broadly refers to a generic substance binding to the N-terminal domain or to the NLS of Vpr, without **any** reference to other properties e.g. the ability to inhibit nuclear import. Even if D1 (see point.2.1 for the summary) discloses and exemplifies several Vpr derived peptides and antibodies binding to the NLS of the HIV-1 protein Vpr only in a theoretical manner, it is not teaching away from the subject-matter of claim 1. In this respect attention is drawn also to pg.7 l.23-24, pg.8 l.3 of D1, where the use of the Vpr- peptides to produce specific antibodies is encouraged. In present case, the skilled person provided with the peptide sVPR21-40 disclosed in D1 can obtain antibody binding thereto, without the exercise of any inventive skills, thereby producing a substance specifically binding to the NLS of Vpr (as disclosed in claim 1). Consequently the subject-matter of independent claim 1 lacks inventiveness and is obvious over the disclosure of D1 (Art.33(3) PCT).

3.2 The same arguments cited for claim 1 are valid, mutatis mutandis, for dependent claims 4-8 of the application. The mere sequencing (claims 7 and 8) is also not adding any unexpected properties to the substances referred to in claim 1. According to the subject-matter of claim 4 and as substantiated in the application, the substance may be a peptide (CDR3) or a scFv. As far as it concerns scFv, one CDR3 sequence is not enough to confer special properties to said scFv, since this definition is very broad and does not limit the scope of the claim to a specific scFv. As far as it concerns the peptides having amino acid seq. ID 2,4,6: example 2 of the application clearly shows that they either do not bind to the NLS of Vpr (seq. ID 2,6), and therefore do not solve the problem of the claim, or they do not inhibit the translocation into the nucleus(seq.ID 4), and therefore do not solve the problem of the application.

3.3 The subject-matter of independent claims 12 and 22 is also not inventive (Art.33(3) PCT) since it refers to mainly standard composition(s) in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

3.4 The subject-matter of claim 13 broadly refers to a method to inhibit the import of a NLS-containing molecule into the nucleus of a cell, using a substance according to claim 1. It is unlikely, and the applicant fails to show, that a substance according to claim 1 is capable of inhibiting the import of all NLS-containing molecule covered by said definition. Consequently the substance according to claim 1 does not solve the problem posed by the claim and does not fulfill the requirements of Art.33(3) PCT.

3.5 The same arguments cited for the subject-matter of claim 13 are valid, mutatis mutandis, for claims 16,17,18 and 21 of the application referring to generic pre-integration complex and viral infection, not limited to the virus disclosed in the application.

3.6 The subject-matter of claim 14 (original claim 17) does also not involve an inventive step in the sense of Art. 33(3) PCT. The document D3, which is regarded as being the closest prior art, discloses cyclic peptide analogs which functionally mimic the NLS of the HIV-1 proteins MA, Vpr, Tat. Present cyclic peptide analogs are candidates for drugs based on blocking nuclear import of the viral genome of HIV and for the therapeutic treatments of HIV infection (see pg. 4 lines 1-8,20-24 and pg.22 lines 14-28). The examples focus on a the production and screening of a cyclic peptide library based on the structure of HIV-1 MA as working example. The general teaching of the document is to target the NLS-containing molecules of HIV-1 MA, Vpr and Tat to inhibit nuclear import of said proteins. Cyclic peptides inhibit nuclear import by a different mechanism compared to antibodies and could result inhibition of cellular functions as well. Nevertheless, antibodies or scFv are simply one of several straightforward alternatives which the skilled person would select, in accordance with circumstances, without the exercise of any inventive skills and merely solve a standard problem, i.e. the improved applicability of said inhibitors. Hence, the subject-matter of claim 14 lacks inventiveness (Art.33(3) PCT). Furthermore, it should be noticed that the subject-matter of present claim is not limited to a method to inhibit Vpr import by means of antibodies (scFv), but broadly refers to "substances". However, as far as it concern antibodies (scFv), identified by only one CDR3, the same arguments as mentioned at point 3.2 apply.

3.7 The subject-matter of claims 19 and 20 contravenes the requirements of Art.33(3) PCT. In the absence of any experimental data, verbal support is not enough to show that said substances solve the problem posed in present claims, namely are useful

to treat said disorders.

3.8 For the assessment of the present claims 13,14,16-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4 **Final Remarks**

4.1 The term "substance" used in claim 1 is vague and unclear and lacks any technical feature, thereby rendering the definition of the subject-matter of said claim unclear (Art. 6 PCT).

4.2 Moreover claim 1 does not meet the requirements of Art. 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, namely by "a substance that specifically binds to....", which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

4.3 Claim 21 is unclear (Art. 6 PCT) since it refers to "a vaccine" which has been deleted in the amended set of claims.